

Flame Retardant Alternatives

Proprietary B: Aryl phosphate

Hazard Review

Proprietary B: Aryl phosphate
Existing Data Summary Table – Human Health Endpoints

✓ = Endpoint characterized by existing data * = Data available but not adequate ✗ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing studies. It does not indicate a positive or negative result for that particular endpoint.

<i>Acute Toxicity</i>	
Oral	*
Dermal	*
Inhalation	
Eye irritation	*
Dermal irritation	*
Skin sensitization	
<i>Subchronic Toxicity</i>	
28-Day oral	*
90-Day oral	
Combined repeated dose with reproduction/developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
<i>Reproductive Toxicity</i>	
Reproduction/developmental toxicity screen	
Combined repeated dose with reproduction/developmental toxicity screen	
Reproduction and fertility effects	

<i>Developmental Toxicity</i>	
Reproduction/developmental toxicity screen	
Combined repeated dose with reproduction/developmental toxicity screen	
Prenatal developmental	
<i>Chronic Toxicity</i>	
Chronic toxicity (two species)	
Combined chronic toxicity/carcinogenicity	
<i>Carcinogenicity</i>	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/carcinogenicity	

<i>Neurotoxicity</i>	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
<i>Immunotoxicity</i>	
Immunotoxicity	
<i>Genotoxicity</i>	
Gene mutation in vitro	*
Gene mutation in vivo	*
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	*
DNA damage and repair	*
Other	*

Proprietary B: Aryl phosphate
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓ = Endpoint characterized by existing data * = Data available but not adequate ✗ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
<i>Bioconcentration</i>	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
<i>Degradation and Transport</i>	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
<i>Aquatic Toxicity</i>	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
<i>Terrestrial Organism Toxicity</i>	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary B: Aryl phosphate

Synonym

CAS

MF

MW

SMILES

Many of the available health effects studies were conducted with commercial mixtures that commonly contained triphenyl phosphate as well as Proprietary B. The available information regarding the composition of these mixtures is presented below, but the composition of the actual samples tested in the health effects studies usually was not reported.

[Formulation 1] is reported to contain 60-100% Proprietary B and 15-40% triphenyl phosphate (Ref. 24) and [Formulation 2] is reported to contain 60-100% Proprietary B and 4-7% triphenyl phosphate (Ref. 25).

Major Components of [Formulation 3] and [Formulation 4] as reported in Ref. 34		
Component	[Formulation 3]	[Formulation 4]
Total Proprietary B	49	61
[Chemical 1]	8	11
[Chemical 2]	6	7
[Chemical 3]	2	5
[Chemical 4]	21	27
[Chemical 5]	12	11
Triphenyl Phosphate	33	18

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as “non-definitive”, possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed in Sprague-Dawley rats (3/sex) given [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) as a single oral dose of 5,000 mg/kg (Ref. 13). Clinical signs, which included tremors (0/3 males, 1/3 females), oral discharge, ataxia (0/3 males, 1/3 females), decreased locomotion (1/3 males, 1/3 females), chromorhinorrhea, chromodacryorrhea, and abdominogenital staining, subsided by day 11. No effects on body weight gain and no gross internal lesions were observed.

A parallel acute oral study on Sprague-Dawley rats (3/sex) given [Formulation 2] at a dose of 5,000 mg/kg, reported clinical signs (abdominogenital staining and chromorhinorrhea) on the first 2 days post dosing, but no mortality, body weight gain effects, or gross internal lesions were reported (Ref. 17).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as “non-definitive”, possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects, the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed among Sprague-Dawley rats (3/sex) that were dermally exposed to [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) at a dose of 2,000 mg/kg for 24 hours under an occlusive covering (Ref. 14). There were no effects on body weight gain, no signs of irritation on the test site, and no gross internal lesions observed.

In a parallel study in Sprague-Dawley rats (3/sex) dermally treated with 2,000 mg/kg [Formulation 2], all but one female gained weight, but there were no deaths, signs of irritation, or gross internal lesions (Ref, 18).

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies were located that followed or were similar to the guideline. A non-guideline study evaluated neurotoxicity of combustion products of an Proprietary B/triphenyl phosphate mixture in the presence of cyclic phosphonate compounds.

Additional Studies and Information:

Preliminary results of a study were reported (Ref. 38) investigating whether toxic compounds were formed when cyclic phosphonate compounds were thermally decomposed in the presence of other phosphate compounds in trimethylol polyol-based urethane foam. When rats were exposed (head only) for 20 minutes to smoke and decomposition gases from foam containing equal proportions of the cyclic phosphonate compounds and a mixture of Proprietary B and triphenyl phosphate, no convulsive seizures, characteristic of exposure to toxic bicyclic phosphites or phosphates, were observed.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as “non-definitive”, although they were consistent with current guidelines.

Additional Studies and Information:

Slight conjunctival erythema was observed in the eyes of 1/1 male and 1/2 female New Zealand White rabbits 24 hours after instillation with 0.01 mL of [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) but was resolved by 48 hours (Ref. 15). No conjunctival discharge or effects on the cornea or iris were observed. The material was tentatively characterized as “practically non-irritating”, based on a maximum irritation score of 1.3/110 at 24 hours.

In a parallel study in New Zealand White rabbits (1 male and 2 females) instilled with 0.01 mL [Formulation 2], there were no signs of eye irritation observed at 1, 24, 48, or 72 hours (Ref. 19). The material was tentatively characterized as non-irritating to the eyes based on a primary irritation index of 0/110 at all timepoints.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies on the Durad materials referred to them as “non-definitive”, although they were consistent with current guidelines.

Additional Studies:

No dermal irritation (erythema or edema) was observed in one male and two female New Zealand White rabbits that were dermally exposed for 4 hours to [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) on two occluded test sites (0.5 mL per site) and examined at 4.5, 24, 48, or 72 hours (Ref. 16). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In a parallel dermal irritation study in one male and two female New Zealand White rabbits exposed for 4 hours to [Formulation 2] on two occluded test sites (0.5 mL per site), no irritation was observed at times between 4.5 and 72 hours (Ref. 20). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In skin irritation assays in male New Zealand White rabbits (6/group), 24-hour topical administration (0.5 mL/site) of [Formulation 4] or [Formulation 10] did not elicit erythema or edema to intact or abraded skin (examined at 24 and 72 hours) (Ref. 6). The mean primary dermal irritation indices were 0/2.0 for both materials, which were characterized as non-irritating to skin.

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The skin sensitization endpoint is not satisfied.

Basis for Conclusion:

No studies were located that followed or were similar to the guideline listed above or otherwise addressed skin sensitization.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A confidential study was submitted that reported preliminary results of a 39-41-day combined subchronic plus reproductive/developmental toxicity screening study in rats exposed by oral gavage. Preliminary results suggested adrenal and liver effects, with adrenal weight effects in females at a LOAEL of 25 mg/kg/day. These data are not adequate because the final results were not available. No other verifiable data were available for defined substances tested under guideline methods. A study on undefined [Formulation 4] appeared to follow the guideline for a 28-day oral study, but was only available as an incomplete robust summary. The unexplained mortality in this study indicates that it may not be an adequate study.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

As described in an incomplete robust summary (results were not presented quantitatively) for an HPV submission, Sprague-Dawley rats (10/sex) received [Formulation 4] in the diet at concentrations of 0, 0.1, 0.5, or 1.0% for 28 days (Ref. 5). Treatment had no effect on survival (but 12 rats died: 1 control, 4 low-dose, 4 mid-dose, and 3 high-dose rats). Treatment also had no effect on urinalysis results, incidence of gross lesions at necropsy, or histology of the liver and kidney (histology examined only in high dose animals and controls). It was not specified whether animals that died during the study were necropsied or examined histologically. Reduced feed consumption was observed in the mid-dose group in both sexes and reduced body weight gain was noted in high-dose females. Abnormalities (not specified) were observed in clinical chemistry measurements in mid- and high-dose groups and in hematology parameters at the high dose. Relative liver weights

were elevated in all treated groups. The unexplained mortality during this short term study raises concern for study adequacy.

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

Subchronic Dermal Toxicity (21/28-day or 90-day)

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90-day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A confidential study was submitted that reported preliminary results of a 39-41-day combined subchronic plus reproductive/developmental toxicity screening study in rats exposed by oral gavage. Preliminary results suggest an ovarian weight effect at ≥ 25 mg/kg/day, and an epididymal weight effect and reduced fertility at 100 and 400 mg/kg/day. These data are not adequate because the final results were not available. No other pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A confidential study was submitted that reported preliminary results of a 39-41-day combined subchronic plus reproductive/developmental toxicity screening assay in rats exposed by oral gavage. Preliminary results suggest reduced pre- and post-natal survival at 400 mg/kg/day. These data are not adequate because the final results were not available. No other pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

No available chronic toxicity data.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

No available carcinogenicity data.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

Additional information

As described in an unvalidated robust summary, 3 days of exposure to [Formulation 7], tested without metabolic activation at concentrations between 0.04 and 5.0 µg/mL, did not induce cell transformation in cultured Balb/c-3T3 cells (Ref. 36).

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Available acute and 28-day studies indicate that there is a risk of delayed neurotoxicity from exposure to Proprietary B. Most studies either were conducted on undefined substances or were not described in sufficient detail. A summary of a study on purified components of [Formulated] flame retardants suggests that [Chemical 4] or [Chemical 2] are the neurotoxic components of these mixtures; however, details of the *in vivo* study in hens were not located. The neurotoxicity of Proprietary B preparations would be dependent on the relative content of [Formulation 11] isomers. No data are available for the full battery of tests for functional neurotoxicity or for developmental neurotoxicity.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The acute study (experiment A) on a defined Proprietary B mixture departed from guideline in that enzyme inhibition was assayed 24 hours after dosing rather than 48 hours, but reported significant suppression of both brain neurotoxic esterase and plasma cholinesterase levels. The longer study did not conduct a complete battery of neurobehavioral tests as stipulated under the guideline, but

reported adverse effects on motor coordination at all doses on the day of treatment. The highest dose (11,700 mg/kg) exceeded that recommended under the guideline, but that deviation does not affect the conclusion of the study. Studies on purified components of [Formulated] flame retardants identified the neurotoxic components, but were not adequately described. The majority of studies suggest that delayed neurotoxicity may result from exposure to oral doses in excess of 1,000 mg/kg.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Acute oral delayed neurotoxicity

Species, strain, sex, number: Hen, 12-14 months old, White Leghorn, 4/dose for experiment A; 10-12/dose for experiment B.

Purity: Proprietary B with the composition as in the following table.

Composition of Proprietary B assayed by Ref. 37	
Component	Percent
Total Proprietary B	<75
[Chemical 4]	24
[Chemical 6]	18
[Chemical 2]	10
[Chemical 7]	10
[Chemical 5]	6
[Chemical 8]	7
[Chemical 9]	<1
Triphenyl Phosphate	24

Doses: Experiment A. Six doses between 12 and 11,700 mg/kg;

Experiment B. 0, 12, or 370 mg/kg in corn oil or 11,700 mg/kg undiluted

Vehicle: Corn oil

Positive control: Tri-*ortho*-cresyl phosphate (TOCP)

Route: Oral (not specified)

Exposure duration, frequency: Experiment A, single treatment followed 24 hours later by biochemical assay; Experiment B, 6 weeks, single treatments 3 weeks apart; study terminated 3 weeks after second dose.

Method: Experiment A. Brain neurotoxic esterase (NTE) and plasma cholinesterase (PChE) measurements recorded 24 hours after single treatment with Proprietary B, corn oil or TOCP.

Experiment B. Doses were chosen based on results of experiment A to represent minimal, 50%, and maximal inhibition of brain NTE. Body weight and food consumption measured every 3-4 days, walking behavior evaluated weekly. Neurohistopathology evaluated at termination.

Results: Experiment A. The NOAELs for inhibition of NTE or PChE were 12 and 180 mg/kg, respectively. Doses about 1,000 mg/kg and higher caused ~70% inhibition of NTE and ~80% inhibition of PChE. The positive control (500 mg/kg of TOCP) inhibited brain NTE by 85.2% and PChE by 70%.

Experiment B. Proprietary B had no effect on mortality. Few adverse signs visible at or below 370 mg/kg. All treated at 11,700 mg/kg showed motor incoordination beginning day 1, with feather loss 7-11 days later. Body weights not affected at lowest dose. Body weight effects at mid- and high-dose are uncertain because text and graph do not match; one dose caused transient weight loss on days 22-38 and the other persistent weight loss from day 22 to the end of the study. TOCP caused persistent weight loss beginning day 5. Food consumption was transiently reduced in all groups (including positive and negative controls) on day 2 and 23, also on day 18 for TOCP. Significant transient, dose-dependent impairment of gait was observed on day 1 and 22 for hens treated with Proprietary B at all doses. Hens treated with TOCP showed significant impairment on day 1 and 15, with gradual worsening to the end of the study. Neurohistopathological examinations revealed no significant difference between Proprietary B treatment and corn oil controls, whereas TOCP caused a significant increase in axonal degeneration in brain, spinal cord (cervical, thoracic and sacro-lumbar), and bilateral degeneration of the sciatic nerve.

Reference: Ref. 37

Additional Studies:

As described in Ref. 44, a series of acute delayed neurotoxicity assays were conducted on [Formulated] flame retardants. No ataxia was observed in groups of 4 hens treated with [Formulation 5] at doses of 2,000, 4,000, or 8,000 mg/kg; 3/30 hens treated with 16,000 mg/kg showed ataxia (Ref. 7). Only 1/10 hens treated with [Formulation 6] at 20,000 mg/kg exhibited ataxia (Ref. 8). In one study on [Formulation 4], no ataxia was observed at doses of 500, 1,000, or 2,000 mg/kg, whereas 2/10 treated at 4,000 mg/kg showed ataxia (Ref. 9); inhibition of brain NTE was 79.5% at the highest dose. In a second study on [Formulation 4], incidences of ataxia (0/10, 3/10, 1/10 and 1/10) and neurohistopathological lesions (1/10, 0/10, 1/10, and 2/10) were not precisely related to the respective doses of 3,000, 5,000, 7,000, and 9,000 mg/kg (Ref. 10). For [Formulation 3], incidences of ataxia (1/9, 4/10, 6/10 and 3/10) and neurohistopathology (0/10, 4/10, 7/10 and 1/10) were observed in the 2,000, 4,000, 6,000, and 8,000 mg/kg groups, respectively (Ref. 11).

A subchronic (91-day) oral neurotoxicity assay is summarized briefly in a TSCA 8e submission (Ref. 12), and in more detail by Ref. 44 and in a robust summary in an HPV submission (Ref. 23; U.S. EPA comments not available). In this study, hens (20/group) were administered [Formulation 3] (mixture of Proprietary B and triphenyl phosphate) daily at doses of 0, 10, 20, 90, and 270 mg/kg/day. Deaths occurred in all dose groups as follows: 2/20 vehicle controls, 4/20 positive controls, 3/20 at 10 mg/kg/day, 5/20 at 90 mg/kg/day, and 6/20 at 270 mg/kg/day. Ataxia was observed in 4/20 at 90 mg/kg/day and 9/20 at 270 mg/kg/day. Histopathological examination of

nervous tissue of 10 hens/group revealed the following: significant degeneration at 3 levels of the spinal cord in 3 vehicle controls, significant degeneration of the spinal cord in TOCP hens, degeneration of the spinal cord and peripheral nerves in hens of the 90 and 270 mg/kg/day groups, with a dose-response relationship for severity and incidence (further details not reported). No ataxia or brain histopathology was observed at 10 or 20 mg/kg/day.

[Formulation 4] and [Formulation 6] were given in two 2,000 mg/kg doses 21 days apart to hens (4/group) (Ref. 22). Neither compound caused body weight effects, clinical signs of neurotoxicity or an increase in gross internal lesions at necropsy (21 days after the second dose). There was no evidence of neurohistopathology in hens treated with [Formulation 4], but one out of four hens treated with [Formulation 6] had unilateral brain lesions at two histological levels.

Proprietary B at tested positive for neurotoxicity in hens treated at three 21-day intervals with 10,000 mg/kg (Ref. 33). Effects included gross paralysis with demyelination confirmed histopathologically.

Several components of the [Formulated] series of flame retardants were isolated to >99% purity and tested at doses as high as 1,000 mg/kg in hens for neurotoxicity and suppression of neurotoxic esterase (Ref. 29). Details of these studies were not located. Three isomers of [Chemical 1] and [Chemical 5] elicited no signs of neurotoxicity and no suppression of NTE levels. [Chemical 5] was also judged to be non-neurotoxic, eliciting no ataxia or other signs of neurotoxicity and insignificant suppression of NTE (-4% or -15%) in two tests. Both [Chemical 2] and [Chemical 4] were positive, eliciting ataxia and neurotoxicity at 1,000 mg/kg, but not at lower doses; [Chemical 2] suppressed NTE by 85% and [Chemical 4] suppressed NTE by 79 and 90% in two assays. The author suggested that neurotoxicity was associated with triaryl phosphates containing a 2-alkyl substituent with an oxidizable alpha-hydrogen.

In a two-hen screening test, a single 1,000 mg/kg dose of [Formulation 3] administered in gelatin capsules to two hens resulted in a 53.1% inhibition of neurotoxic esterase activity in the brain (Ref. 42). The report was not clear as to the day on which the hens were sacrificed.

No neurotoxicity studies were located that followed or were similar to the guidelines listed below.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat) OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent) OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred) OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Other Neurotoxicity Data

Cholinesterase inhibition

[Formulation 3] at doses of 15, 20, or 25 mL/kg did not inhibit blood cholinesterase activity, but neither species of animal (3/group) nor the specific biological material assayed were reported (Ref. 4).

IMMUNOTOXICITY

Conclusion:

No available immunotoxicity data.

Basis for Conclusion:

No immunotoxicity study was located that followed or was similar to the guideline listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable genotoxicity data were located. The available studies were only accessible as robust summaries in a IUCLID Dataset that had not undergone review by the European Commission (Ref. 3). Furthermore, the data were unpublished industry-sponsored studies on commercial products for which no contemporaneous component analyses were provided. Current compositional information taken from MSDS documents are presented in the following table. The results of these studies are summarized below despite their uncertain validity. In general, not enough details were provided to ascertain whether protocols met the standards of OPPT or OECD guidelines.

Percentage of Proprietary B and triphenyl phosphate in Currently Available Commercial Products			
Product	Proprietary B (%)	triphenyl phosphate (%)	Reference
[Formulation 7]	60-100	15-40	Ref. 26
[Formulation 8]	60-100	10-30	Ref. 27
[Formulation 9]	60-100	7-13	Ref. 28
[Formulation 2]	60-100	4-7	Ref. 25

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

As described in unvalidated robust summaries, negative results were reported for mutagenicity assays in *Salmonella typhimurium* with or without metabolic activation. [Formulation 7] and [Formulation 9] were tested in strains TA98, TA100, and TA1537 at concentrations as high as 1.62 mg/mL (Ref. 1, 2). [Formulation 9] and [Formulation 2] were tested in strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations as high as 0.1 mL per plate (Ref. 31, 32).

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

As described in an unvalidated robust summary, [Formulation 7] at concentrations of 0.0013-0.1 µL/mL was not mutagenic to cultured mouse lymphoma L5178Y TK^{+/+} cells without metabolic activation (Ref. 30). Results in the presence of metabolic activation were equivocal in that a dose-response was observed, but none of the cultures exhibiting >10% total growth had mutant frequencies 2-fold greater than background.

Gene Mutation in Vivo

- **Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275)**

As described in an unvalidated robust summary, [Formulation 7] (32.5, 75, or 150 mg/mL) fed to adult male fruit flies for 3 days did not induce heritable mutations (Ref. 43).

Chromosomal Aberration in Vitro

No pertinent studies were located.

Chromosomal Aberration in Vivo

- **Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)**

As described in an unvalidated robust summary no increase in chromosomal aberrations was observed in the bone marrow of Chinese hamsters (8/sex/group), 16, 24, or 48 hours after receiving a single oral dose of 5,000 mg/kg [Formulation 7] by gavage (Ref. 41). The summary indicated that the study was conducted under OECD Guideline 475 and GLP. Another unvalidated robust summary reported that a significant increase (compared to controls) in the incidence of bone marrow cells with chromosomal anomalies was observed in Chinese hamsters (6/sex/group) 24 hours after receiving the second of two consecutive daily doses of 2,500 or 5,000 mg/kg/day [Formulation 7] by oral gavage (Ref. 40); no increase was observed in animals receiving 1,250 mg/kg/day.

DNA Damage and Repair

- **Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)**

As described in an unvalidated robust summary, [Formulation 7] tested without metabolic activation at concentrations between 0.6 and 75 nL/mL did not cause unscheduled DNA synthesis in cultured rat hepatocytes (Ref. 35).

Other

- **In vivo Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5915)**

As described in an unvalidated robust summary, there was no increase in the frequency of sister chromatid exchanges in bone marrow cells of Chinese hamsters (4/sex/group) 24 hours after receiving a single oral dose of 1250, 2,500, or 5,000 mg/kg [Formulation 7] by gavage in carboxymethylcellulose (Ref. 39).

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

Summaries were located for several acute toxicity studies of Proprietary B in an HPV test plan submission and accompanying robust summaries (Ref. 23); however, EPA comments on this submission were not available. The summaries included two 96-hour studies in fathead minnows (*Pimephales promelas*), three 96-hour studies in rainbow trout (*Oncorhynchus mykiss*), and three 48-hour studies in *Daphnia magna*. According to Ref. 21, all of the studies were conducted with 100% Proprietary B; however, other reports have identified the tested material in some of these studies as [Formulation 1] (Ref. 24) or [Formulation 4] (Ref. 21). [Formulation 1] is a mixture containing 60-100% Proprietary B and 15-40% triphenyl phosphate (Ref. 24). [Formulation 4] has been reported to contain 61% Proprietary B and 18% triphenyl phosphate (Ref. 34; see table at beginning of Human Health Effects for details). The available study summaries and Material Safety Data Sheets are insufficient to precisely establish the composition of the materials tested in the acute toxicity studies. Without precise knowledge of the composition of the tested materials, it is not possible to use these studies to make a definitive statement regarding the acute toxicity of Proprietary B. The publicly available information regarding the acute toxicity of Proprietary B to freshwater fish or aquatic invertebrates is insufficient to satisfy the endpoints in the guideline protocols listed below.

A confidential study was submitted that reported a freshwater daphnid 48-hour EC₅₀ >0.77 mg/L, the maximum test concentration. This concentration is above the water solubility limit of Proprietary B.

A confidential study was also submitted that reported a freshwater green algal 72-hour EC₅₀ of approximately 0.480 mg/L. This concentration is above the water solubility limit of Proprietary B. The available data were judged inadequate to meet this endpoint

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**

- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

No available chronic toxicity data for fish or aquatic invertebrates.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

No available acute and subchronic toxicity data for terrestrial organisms.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary B

CAS

MF

MW

SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation:

Conclusion:

The available aerobic biodegradation data are not adequate.

Basis for Conclusion:

A single confidential ready biodegradation study, indicating that Proprietary B is not ready biodegradable, was submitted. This study is not sufficient to fully characterize the aerobic biodegradation of Proprietary B under environmental conditions.

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data